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Original Research Article

Efficacy of Glycosylated Fibronectin (GlyFn) Estimation in Prediction of the Severity of Disease in New Onset Hypertension in Pregnancy from 24 Weeks to Term: A Cross Sectional Study

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Conflict of interest: Nil

Abstract:

Background: As hypertensive disorders of pregnancy contribute significantly to maternal and neonatal mortality and morbidity, it is very essential to diagnose which cases will eventually have severe disease. Glycosylated fibronectin (GlyFn) is a protein involved in vessel remodelling and inflammation. It is a new biomarker to diagnose severe disease in new onset hypertension. The objective is to determine the sensitivity, specificity, positive predictive value and negative predictive value of GlyFn to predict the severity of disease in new onset hypertension in pregnancy from 24 weeks to term.

Methods: The study was carried out in the Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar from April 2023 to December 2023. A total of 50 cases from 24 weeks to term with new onset hypertension were enrolled. The glycosylated fibronectin was estimated in their serum. Final analysis was done on 30 cases, of less than 37 weeks diagnosed as pre-eclampsia.

Results: In 30 mothers with PE: 28 true positive, 2 false negative. TPR (true positive rate) or sensitivity = 28/30 = 93.33%; FNR (false negative rate) = 2/30 = 6.67%. Besides, all the high positive cases were associated with adverse maternal and fetal outcomes such as severe hypertension, thrombocytopenia, increased liver enzymes, increased creatinine, neurological complications, pulmonary edema, and low birth weight, prematurity, growth restriction and intrauterine death.

Conclusion: All the high positive cases were associated with severe maternal and fetal adverse outcomes and therefore we recommend that cases with GlyFn level more than 600 µg/mL be considered for hospital admission and intensive maternal and fetal monitoring and termination accordingly.

Keywords: Hypertensive disorders of pregnancy, glycosylated fibronectin, new onset hypertension, novel biomarker.

Introduction

While significant advances have been made in understanding how various diseases impact on pregnancy, hypertensive disorders in pregnancy with its numerous complications still remain an enigma. The exact timing of delivery remains elusive. As proteinuria is no longer an essential criteria for cases to be diagnosed as pre-eclampsia (NICE, 2019) [1], there is a need for an effective biomarker that can be easily estimated in maternal serum to predict adverse maternal or fetal outcome.

A new biomarker which has been used a predictor of preeclampsia is glycosylated fibronectin (GlyFn). Fibronectin is a protein involved in vessel remodelling and inflammation (Rasanen, 2015) [2]. Nagalla et al [3] designed a study to assess GlyFn as a point-of-care test to rule-in or rule-out preeclampsia and showed promising results. Rasanen et al [2] studied the ability of GlyFN to assess pre-eclampsia status and analysed the relationship between GlyFn and pregnancy outcomes. They found GlyFn to be a robust biomarker for diagnosis and prognosis of pre-eclampsia. This is an exploratory study that aims to assess the efficacy of GlyFn to predict the severity of disease in new onset hypertension in pregnancy from 24 weeks to term.

Specifically, the question it attempts to answer is "What is the sensitivity, specificity, positive predictive value and negative predictive value of GlyFn in detecting cases with preeclampsia?"

Material and Methods

The study was carried out in the Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College and Hospital from April 2023 to December 2023. A total of 50 patients were enrolled in the study, with new onset hypertension from 24 weeks onwards. Patients with blood pressure of systolic more than or equal to 140 mm Hg and/or diastolic more than or equal to 90 mm Hg on two occasions measured four hours apart, irrespective of proteinuria, maternal organ dysfunction or uteroplacental dysfunction were included. Cases with known diabetes, collagen vascular disease, renal diseases, chronic hypertension and patients on aspirin were excluded.

Pre-eclampsia is defined as per NICE (2019)1definition.

The glycosylated fibronectin was estimated in their serum by using the LumellaTM test (DiabetOmics, Inc.) according to the manufacturer's instructions. Test strips were configured with monoclonal antibodies against GlyFn labelled with gold particles for quantification using a hand held LumellaTM reader system. Under all aseptic and antiseptic conditions, 5 µl of serum is diluted 1:350 in running buffer and 120 µl of diluted serum is added to test strip and inserted into the reader. The GlyFn concentration is displayed on the reader at the end of 10 minutes. Calibration information is supplied by the manufacturer as a lot-specific radiofrequency identification (RFID) tag on each test kit.

The instrument is calibrated before each test using a calibration strip provided by the manufacturer. The manufacturers do not recommend testing beyond 37 weeks as the results are not standardised but we have done it in our study although, the final analysis has been made on the cases less than 37 weeks. The test is reported in the range as shown below (table 1):

Table 1: Test results according to GlyFn range

GlyFn Range (microgram/mL)	Test result
50-250	Normal
251-350	Abnormal
351-600	Positive
>600	High positive

Once new onset hypertension was detected, GlyFn was tested and the following investigations were conducted -haemoglobin, platelet count, AST, ALT, serum creatinine, LDH, uric acid were done. Ultrasound with doppler study of umbilical artery was done. The patients were managed as per the hospital protocol and followed upto delivery. To prevent any bias, the consultant physicians were not informed about the GlyFn value.

One patient came in the emergency as 34 weeks 5 days pregnancy with hypertension in pregnancy (BP: 140/90 mm Hg) in preterm labour and GlyFn was measured (high positive). It was later found she delivered a 3.8 kg baby who had shoulder dystocia during delivery and expired 14 hours after birth in NICU. She tested positive for diabetes as well. Two other patients could not be followed up with. Therefore, the total number of patients enrolled in the study at the time of data analysis was 47.

30 patients, of gestational age less than 37 weeks were diagnosed as pre-eclampsia or having severe disease as per the NICE (2019)1 guidelines. The final analysis was done on these patients.

Results

Table 2 shows the association of risk factors like primiparity, family history of hypertension and history of hypertension in previous pregnancy with GlyFn.

Table 2: Association of GlyFn to risk factors

GlyFn value	No. of cases	Risk factor present	Risk factor absent
Normal (50-250)	3	1	2
Abnormal (251-350)	13	11	2
Positive (351-600)	19	13	6
High positive (>600)	12	9	3

We can observe from table 3 that 33.33% of patients with normal GlyFn value had severe hypertension and 62.96% of patients with abnormal, positive and high positive GlyFn had severe hypertension. It is observed that 46.15% and 58.33% of positive and high positive GlyFn had severe hypertension.

Table 3: Association of GlyFn with blood pressure

GlyFn value	No. of cases	BP 140/90-159/109 mmHg	BP ≥160/110
Normal (50-250)	3	2(66.66%)	1(33.33%)
Abnormal (251-350)	13	9(69.23%)	4(30.76%)
Positive (351-600)	19	13(68.42%)	6(46.15%)
High positive (>600)	12	5(41.66%)	7(58.33%)

Table 4 shows that the average time of testing or time of presentation of hypertension in the abnormal, positive and high positive group is 35.64 weeks of gestation which is almost same as that of the normal group that is 35.33 weeks. The average time of delivery of the abnormal, positive and high positive group is 36.49 weeks which is quite similar to the normal group that is 36.66 weeks. However, it must be noted that one patient in the high positive group was a primigravida, 35 years, who developed hypertension at 25 weeks and had blood pressure 160/100 mm Hg at the time of admission. Her platelet count was 151000, AST 43 U/L, ALT 12 U/L, LDH 1420 and at 26 weeks there was intrauterine fetal death. Following expulsion, her blood pressure was controlled on medication.

Table 4: Level of GlyFn with gestational age

GlyFn Value	No. of cases	Avg. Gest. Age inweeks at the timeof testing (time ofonset of hypertension)	Avg. Gest. Age in weeks at the time of delivery	Range of time from diagnosis to delivery in days
Normal	3	35.33	36.66	4-5
Abnormal	13	35.69	36.58	0-19
Positive	19	36.66	37.28	0-29
High positive	12	34.58	35.33	0-28
Total	47			

Association of GlyFn with maternal and fetal complications is shown in table 5. There were no cases with abruptio placentae, HELLP, DIC or stillbirth.

Table 5: Association of GlyFn with complications

Parameters		Normal	Abnormal	Positive	High positive
Maternal Complications	Creat>1.02	0	0	0	2
	AST/ALT>40	1	9	8	5
	Neurological complications	0	0	1 (eclampsia)	2
	Plt count<150	0	2	4	3
	Pulmonary edema	0	1	0	1
Fetal Complications	NICU admission	0	1	5	5
	Prematurity	1	5	5	6
	IUD	0	0	0	1
	IUGR	1	2	7	8

We divided the patients into two groups depending on whether preeclampsia or adverse outcome was present or absent.

We measured sensitivity, specificity, positive predictive value and negative predictive value of GlyFn before 37 weeks in the cases diagnosed as pre-eclampsia. There were 30 such cases. Clinical characteristics of these 30 cases are given below in table 6.Lumella results in 30 mothers with PE: 28 true positive, 2 false negative.

TPR (true positive rate) or sensitivity = 28/30 = 93.33%, FNR (false negative rate) = 2/30 = 6.67%

Table 6: Clinical characteristics

Clinical characteristics	Units	Overall (n=30)
Age [mean (SD)]	years	26.93(5.17)
Gestational age [mean(SD)]	weeks	33.86 (2.43)
SBP [mean(SD)]	mm Hg	155.67(20.12)
DBP [mean(SD)]	mmHg	99.33(10.15)
Proteinuria [number (%)]		6(20.7)
Hemoglobin [median(IQR)]	gm/dL	10.50(9.80,10.70)
Platelets [median(IQR)]	10^3/uL	169.00(139.00,248.00)
AST [median(IQR)]	U /L	45.50(32.50,79.25)
ALT [median((IQR)]	U /L	30.00(24.25,81.75)

Creatinine [median(IQR)]	mg/ dL	0.60(0.49,0.60)
LDH [median(IQR)]	U /L	290.00(261.00,341.00)
UA [median (IQR)]	mg/ dL	5.10(4.40,6.60)
Birth weight [mean(SD)]	Kg	2.20(0.63)
Preterm [number (%)]		18(64.3)
Low birth weight [number (%)]		19(65.5)
SVD [number (%)]		15(50.0)

Discussion

Rasanen et al [2] had done a longitudinal cohort study and evaluated maternal serum glycosylated fibronectin as a point of care biomarker for assessment of preeclampsia. They found significantly higher levels of GlyFn in first trimester in women with preeclampsia and it remained high throughout pregnancy. Increased GlyFn was significantly associated with preterm birth, increases in blood pressure, uric acid and alanine transaminase and small for gestational age neonates.

Repeated measurements showed that weekly change in third trimester was 81.7 µg/mL in mild pre-eclampsia versus 195.2 µg/mL for severe pre-eclampsia, so disease progression is associated with increasing levels of GlyFN, making it useful for prognosis. They found best sensitivity and specificity as a predictor of preeclampsia at a cutoff of GlyFn at176.4 µg/mL. Huhn et al [4] studied the performance of Glyfn as a short term predictor of preeclampsia. They included the patients with risk factors for pre-eclampsia and patients with clinical suspicion of pre-eclampsia. The patients diagnosed as having pre-eclampsia were excluded. They considered the threshold of GlyFn at 315 µg/mL and found sensitivity of 91 % and specificity of 86% for the prediction of pre-eclampsia. Nagalla et al [3] analysed 151 samples with clinical suspicion of preeclampsia and found 32 of 151 (21%) women developed a clinical diagnosis of PE within 4 weeks. They found that GlyFn showed 91% sensitivity, 87% specificity, 64% PPV, 97% NPV. Our study has included patients with and without preeclampsia. The threshold we have taken is 250 µg/mL, which is less than the cut-off taken by Huhn et al [4] and more than Rasanen et al [2]. We have categorised abnormal, positive and high positive results as increased GlyFn. The sensitivity of 93.33 % is comparable to the other studies.

However, in this study it is seen that all the high positive cases were associated with severe maternal and fetal adverse outcomes and therefore we recommend that cases with GlyFn level more than 600 µg/mL be considered for hospital admission and intensive maternal and fetal monitoring and termination accordingly.

Conclusion

As fibronectin is a new biomarker, it's role in the pathogenesis of preeclampsia and the utilisation as a predictor remains much to be discovered. This is an exploratory study to determine the efficacy of GlyFn in diagnosing cases with preeclampsia. We found that cases with GlyFn > 600 microgram/L were associated with serious maternal and fetal adverse outcome. Therefore, we recommend that such cases be hospitalised for intensive maternal and fetal monitoring and terminated accordingly.

Some cases with abnormal and positive levels of GlyFn have been associated with adverse outcomes and we recommend management on individual case basis. Normal range of GlyFn was observed in very few cases and it is suggested to do further case control studies to note the level of GlyFn in age and risk factor matched controls. Sensitivity of the test is 93.33 %, therefore there are less number of false negatives.

This analysis was done on 30 cases and therefore, to have a better measurement of this test, we suggest designing a study on a larger sample size.

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